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Correlation Between Demographic and Tumor Characteristics in Non-melanoma Skin Cancers Submitted to Mohs Micrographic Surgery

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Abstract. *Background/Aim: Non-melanoma skin cancer (NMSC) is the most prevalent type of cancer in adults. Surgery remains the golden-standard treatment for this disease. Mohs micrographic surgery (MMS), a surgical technique, is based on the three-dimensional histopathological examination of the margin and surgical bed, layer by layer, in the excised tissue allowing for the determination of the location of the residual tumor, for its complete excision, with high cure rates and preservation of the unaffected tissue. The aim of this study was to present the epidemiological characteristics of the population that was submitted to MMS, as well as, correlate these characteristics with the characteristics of the tumor itself and the surgical procedure. Patients and Methods: A retrospective cross-sectional study was conducted over a 10-year period with an analysis of patient medical records submitted for MMS at the Department of Dermatology of the ABC School of Medicine. Data were presented and evaluated by non-parametric and parametric analyses, using absolute and relative frequency values for the continuous variable, to which a Chi-square test was applied for the verification of power with a significance level of 5%. For the independent variables, the Student's t-test was used to compare means, with a confidence interval (CI) ranging from 95 to 99%, and Friedman's test was used to verify if there were significant differences in the variables of interest. Results: Female patients accounted for 67% of all enrolled patients (n=335). The mean age was 67 years (SD±12.04; median=68; range=25-93 years). The predominant skin phototype (Fitzpatrick's classification) was phototype II (n=228, 46%). All procedures were performed under local anesthesia. Flap reconstruction was the most predominant surgery type (n=17, 68%). The mean number of MMS's stages was 1.6 (range=1-8). There was a mean of 3.8 fragments of skin tissue (range=1-29) per stage. The mean tumor size was 30 mm (92%). This was associated with female sex (p=0.03), H-zone area (p<0.001), flap reconstruction (p=0.004), tumor removal 7 to 12 months after diagnosis (p<0.001) and non-recurrence tumors (p=0.02). Conclusion: NMSCs were frequently observed in older women with skin phototypes II/III. Reconstruction of the primary defect was feasible under local anesthesia, even in tumors with a marked diameter, decreasing the morbidity of this surgery, providing very satisfactory functional and aesthetic results, reduction costs and ease of access to the surgical procedure.*

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Key Words: Non-melanoma skin cancer, epidemiology, Mohs micrographic surgery.

Non-melanoma skin cancer (NMSC) is the most prevalent type of cancer in adults (1, 2). NMSC refers to keratinocytic carcinomas classified as basal cell carcinoma, squamous cell carcinoma and Bowen's disease (3). Surgery remains the gold-standard treatment for this disease. Mohs micrographic surgery (MMS) is replacing the excision and destruction of NMSC in the head, neck, hands, feet and genitalia, due to its advantage in providing high cure rates, preserving normal tissue and optimizing the aesthetic aspects (4).

The objective of the study was to reveal the epidemiological characteristics of the population that was submitted to MMS, as well as, correlate these characteristics with the characteristics of the tumor itself and the surgical procedure.

Table I. *Histopathological types of basal cell carcinomas and squamous cell carcinomas.*

Histopathological subtype in the database	WHO Histological Classification
BCC	BCC
Superficial, multifocal BCC	Superficial BCC
Nodular BCC, solid and nodule-cystic BCC	Nodular BCC (solid)
Micronodular BCC	Micronodular BCC
Sclerodermiform or morpheaform BCC	Infiltrative BCC
Basosquamous BCC	Basosquamous carcinoma
Cystic, adenoid, infundibulocystic, pigmented, mixed (of clear cells, signet ring, granule cells, giant cells, adamantinoid, neuroendocrine and schwannoid differentiation) BCC	Other variants
SCC	SCC
Bowen's disease	Bowen's disease (carcinoma in situ)

WHO, World Health Organization; BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

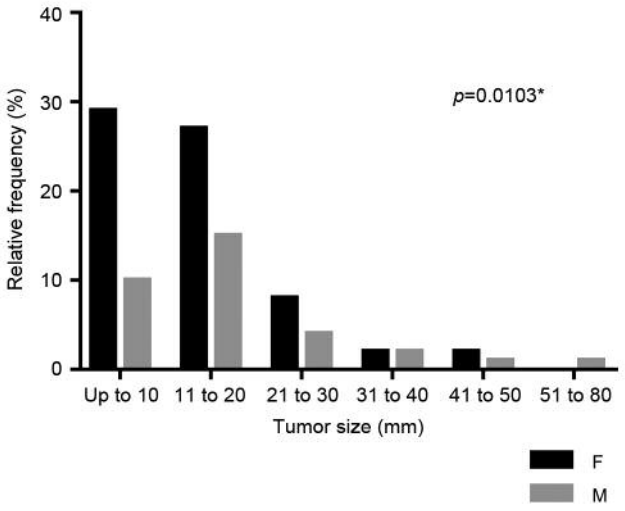

Figure 1. *Relative frequency of non-melanoma skin cancer stratified by sex and pre-surgical tumor size in millimeters (mm). *Chi-square test.*

Patients and Methods

A retrospective cross-sectional study was performed with an analysis of patients' medical records submitted for MMS at the Dermatology Service of the ABC School of Medicine, Santo André, Brazil, over a 10-year period, between May 2005 and May 2015. The project was approved by the Research Ethics Committee of the ABC School of Medicine (No. 58249916.0.0000.0082).

A total of 498 cases were selected out of 1,265 MMS cases. Data such as sex, age, patient skin phototype (according to the Fitzpatrick's classification), type of anesthesia, previous tumor evolution time until surgery, presence of tumor recurrence, tumor topographic location, intraoperative histological type, tumor size, surgical defect size, number of fragments of skin tissue excised during MMS, number of MMS's stages required for complete surgical excision, and type of reconstruction performed, were collected. All patients submitted to MMS in the period declared above were included in the study. Exclusion criteria were: (i) excision of skin tumors by techniques other than MMS, (ii) MMS performed outside the study period, and (iii) missing medical record data.

Data analysis. Regarding cancer location, we divided the cases into three areas according to the parameters of The National Comprehensive Cancer Network (5). H-zone - face (central face, periorbital area, eyelids, eyebrows, nose, perilabial area, lip, chin, pre- and post-auricular skin, temples, ears), genitals, hands and feet; M-zone - cheeks, forehead, scalp, neck and pre-tibial region; L-zone - Trunk and extremities (excluding pre-tibial, ankles, nail, hands and feet).

The MMS stages and the number of fragments of skin tissue excised during MMS were grouped into three categories: (i) ≤1, (ii) 2-4 and (iii) ≥5. Tumor evolution time was stratified into five groups: (i) ≤6 months, (ii) 7-12 months, (iii) 13-24 months, (iv) 25-60 months, and (v) >60 months. For basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), data are presented using the histological classification of the World Health Organization (WHO) (6). In the case of mixed patterns, classification was performed in consideration of the most aggressive pattern according to the literature. Table I shows the histopathological classification adopted in this study.

Statistics. The data were presented and evaluated by non-parametric and parametric analyses, using absolute and relative frequency values for the continuous variable, to which a Chi-square test was applied for the verification of power with a significance level of 5%. For the independent samples, the Student's *t*-test was used to compare means, with a confidence interval (CI) ranging from 95-99%, and Friedman's test was used to verify if there were significant differences in the variables of interest. Software R version 3.4 was used for the analysis. Figures were made use GraphPad Prism 7.0®.

Results

Female patients accounted for 67% of all enrolled patients (n=335) and male patients for 33% (n=163). The mean age of participants was 67 years (SD±12.04; median=68; range=25-93 years). All procedures were performed under local anesthesia. The predominant skin phototype (Fitzpatrick's classification) was phototype II (n=228, 46%), followed by phototype III (n=177, 35%).

Regarding relapse, 95% (n=473) of cases did not show clinical or anatomopathological evidence of occurrence prior to MMS. In the context of recurrent tumors, 80% (n=20) of patients were females, with more aggressive tumors (basosquamous, infiltrative and micronodular BCC and SCC) observed in 68% (n=17) of cases and a mean evolution time

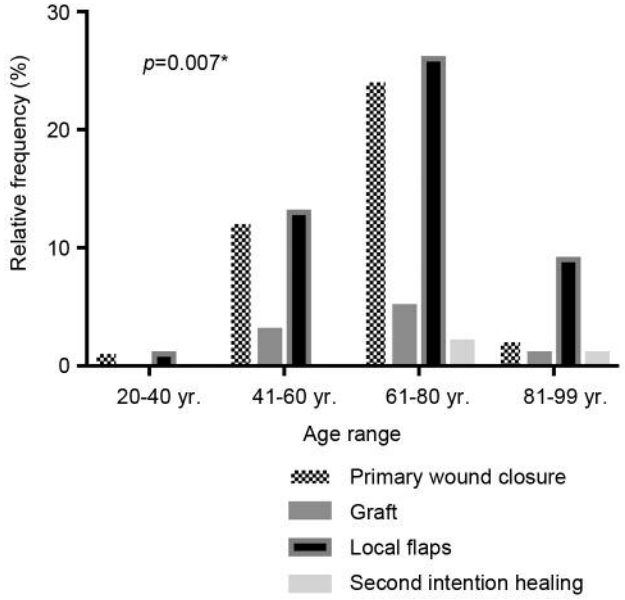

Figure 2. *Absolute frequency of reconstruction types stratified by age group. *Friedman's test.*

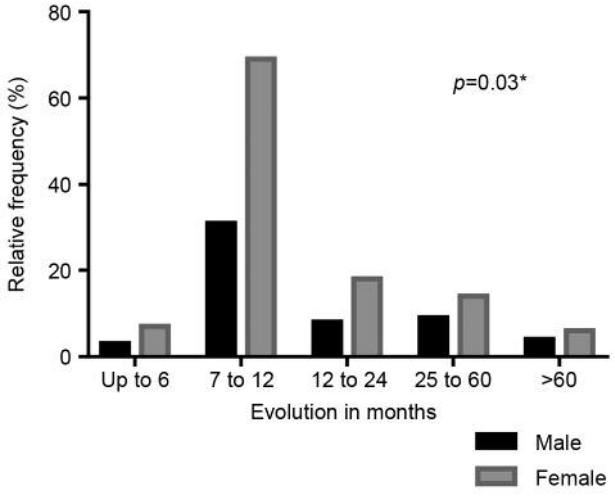

Figure 3. *Non-melanoma skin cancer cases stratified by sex and evolution time (in months) between lesion onset and surgical procedure. *Student's t-test.*

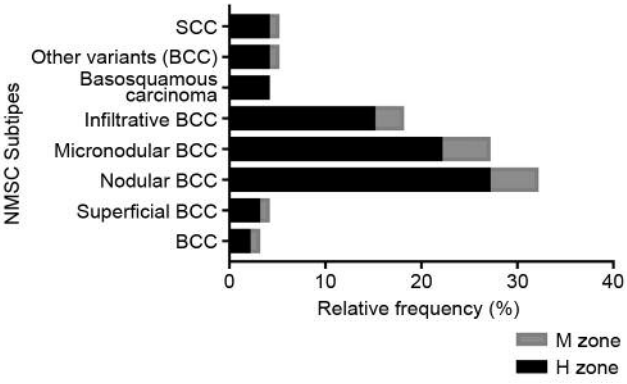

Figure 4. *Frequency of non-melanoma skin cancer according to its subtypes and affected body areas. BCC, Basal cell carcinoma; SCC, squamous cell carcinoma; NMSC, non-melanoma skin cancer.*

of 25-60 months (40%). Flap reconstruction was the most predominant surgery type, accounting for 17 of cases (68%). Overall, the mean number of MMS stages was 1.6 (range=1-8), with a total of 823 stages across the 498 cases. There was a total of 1,900 fragments of skin tissue in the samples, with a mean of 3.8 fragments of skin tissue (range=1-29) per stage. Most of the cases (99.1%) were resolved with up to four MMS stages; 48.5% (n=242) of these were resolved with one stage and 50.6% (n=252) with two to four stages.

Figures 1, 2, 3 and 4 show characteristics of tumors and patients in this study. Table II shows the frequencies and correlations between tumor size and variables such as sex, tumor location, MMS stages, evolution, relapse and reconstruction.

Discussion

Healthcare is influenced by different patient characteristics, such as sex, age, knowledge of disease prevention, and presence of chronic disease (7). In our study, female predominance was observed, and lesions with a size ≤30 mm were the most commonly occurring in this group; a significant association existed. This is in contrast to previous studies in which men accounted for 59.6% and 58.6%, respectively, of all the cases (8, 9). Thompson *et al*. reported that sex had a significant impact on mental and physical healthcare, indicating that women visited their doctors much more frequently than men. Thus, the predominance of women in our study is compatible with the attendance to healthcare services reported by other authors (10-12).

Consistent with our study, Córtes-Peralta *et al*. also found that the mean age of the patients was 64.3 years, while Wain *et al*. reported a mean age of 63.4 years. Similarly to our study, in a two-year study on modified Slow Mohs technique (three-dimensional histology method, but with a conventional analysis time on fixed tissue) by Wollina *et al*., all procedures were performed under local anesthesia (13, 14). The possibility of performing surgery, such as MMS, with a high cure rate, under local anesthesia, constitutes a significant advance in terms of the prevention of intra- and postoperative complications in elderly patients, as observed in our studied cohort, in which 57% of patients were aged 61-80 years, in whom comorbidities occurred more frequently and the use of multiple medications was also common.

Table II. *Relative frequency and association of demographic and tumor variables with non-melanoma skin cancer tumor size.*

Variables	Tumor size (mm)						*p*-Value*
	≤30		>30		Total		
	n	%	n	%	n	%	
Gender							
Male	141	28.3	22	4.4	163	32.7	0.003*
Female	317	63.6	18	3.6	335	67.2	
Location							
H zone	380	76.5	25	4.8	405	81.3	<0.001*
M zone	76	15.2	12	2.41	88	17.6	
L zone	2	0.6	3	0.4	5	1	
Reconstruction							
Flap	223	44.7	19	3.8	242	48.5	0.004*
Primary	186	37.3	10	2	196	39.3	
Graft	37	7.4	10	2	47	9.4	
2nd round	12	2.4	1	0.2	13	2.6	
Evolution (months)							
≤6	49	9.8	1	0.2	50	10	<0.001*
7-12	153	31	4	0.8	157	31.5	
13-24	118	23.7	9	1.8	127	25.5	
25-60	104	21	13	2.6	117	23.4	
>60	34	6.8	12	2.4	46	9.2	
Surgical phases							
1	226	45.3	16	3.2	242	48.5	0.092*
2-3							
222	44.5	21	4.2	243	48.8		
>4	10	2	3	0.6	13	2.6	
Relapse							
No	438	88	35	7	473	95	0.024*
Yes	20	4	5	1	25	5	

*Chi-square test.

In the Northeast Brazil, Aracaju, the predominant skin phototypes (Fitzpatrick's classification), were types II (41%) and III (36%); these values are similar to those observed in our cohort of patients from Southeast Brazil (15). Differences in the BCC incidence rate illustrate the effect of skin phototype on the disease's geographical distribution and incidence, worldwide. This theory is best supported by the low rates observed in countries near the equatorial area, such as Singapore, corroborated by only one case of BCC in our case series belonging to phototype V (16).

Several tumor characteristics are associated with high relapse rates, including location, histological subtype (morpheaform, infiltrative, micronodular and basosquamous), perineural and perivascular infiltration, lack of well-defined clinical margins, and incompletely excised or recurrent lesions (17). Our sample included almost all types of patients, including non-recurrent NMSC patients, who showed a significant association with lesion sizes up to 30 mm.

MMS enables the surgeon to map the location of all tissue removed and microscopically examine the entire deep and lateral margins of a horizontally sectioned specimen (18). This is useful for tumors located in the peripheral areas of orifices, tumors with a high risk of relapse, and tumors that are macroscopically indistinguishable border or of diffuse type (15, 18), in addition to those with a micronodular and infiltrative histopathologic type (10), which accounted for 46% of the BCCs excised in this study. In our study, there was a strong association between tumors ≤30 mm in size that were predominant in H zone, and the nodular, infiltrative or micronodular histopathological patterns;

Contrary to our study, in which only 10% of the cases were submitted to the procedure within the first 6 months after NMSC diagnosis, the mean waiting time for MMS in a study by Diehl *et al.* was 133 days (17). Changes in the largest diameter had no correlation with the time until surgery, suggesting that the growth of small BCCs may not be linear (19). Diehl *et al.* identified 179 cases (63%) with a diameter smaller than 1 cm at diagnosis, and no significant association was observed between waiting times greater than 1 year and surgical defect size. Our study provides

evidence suggesting that the time between diagnosis and MMS is influenced by female sex, with a predominance of tumors up to 30 mm in size and an evolution time of 7-24 months (54%).

Reconstruction type is one of the factors that contributes to patient self-esteem. In our study, flap-type reconstructions were the most prevalent, especially for lesions up to 30 mm in size, and this was statistically significant. In a study by Català *et al*., 58.4% of cases had reconstruction with local flaps followed by 21.9% with primary suture (20).

There is no strong belief that tumor size alone predisposes a patient to a higher number of MMS stages, and large well-delimited tumors can be removed in one stage or a few stages (21). Alam *et al*. analyzed 2,000 cases of MMS with a mean of two stages, and 98.2% of the tumors were resolved in up to four stages (22); these values are very close to those observed in our study. They also identified that the anatomical location influenced the number of stages ($p<0.001$), with the highest number of MMS stages being required for tumors in the nose and ear (22). There is no correct number of stages in MMS for NMSC removal (2). We found no significant association between the number of MMS stages and tumor size, and these variables were, therefore, independent and uncorrelated in this study.

This study has limitations, such as its retrospective nature and its reflection of the experience of a regional service; The therapeutic success obtained in our study encourages the qualification of dermatologists in MMS performance to offer better care to NMSC patients.

Conflicts of Interest

The Authors state that they have no conflicts of interest in regard to this study.

Authors' Contributions

Ellem Weimann: Concept and design of study or acquisition of data or analysis and interpretation of data; drafting of the article or revising it critically for important intellectual contente. Caroline Brandão: Concept and design of study or acquisition of data or analysis. Luiz Terzian: Final approval of the version to be published. Francisco Paschoal: Final approval of the version to be published. Carlos Machado Filho: Final approval of the version to be published. Paulo Criado: Drafting the article or revising it critically for important intellectual content and Final approval of the version to be published.

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